2019 Basic and Clinical Aspects of Dystonia RFA

# Grant Application Cover Sheet

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| **Project Information** | | | | | | | | | | |
| Title: | A next generation sensing neural interface study for adaptive DBS in dystonia | | | | | | | | | |
|  |  | | | | | | | | | |
| Proposed Start Date: 3/1/2019 |  | | | | Total Budget: | | $160,000 | | | |
| Are Human Subjects Involved? | | Yes: | No: | Provide Date of IRB Approval, if yes: | | | | |  | |

2019 Basic and Clinical Aspects of Dystonia RFA

Grant Application Cover Sheet

Have you ever been supported by the Foundation? Yes:  No:

If yes, list the title of the project(s), award amount and briefly describe the results of your research:

NA

Have you or do you plan to submit this or a similar proposal to another agency for funding? Yes:  No:

If yes, provide the title of the project and the name of the agency:

We plan to use this study to create the data that would build towards a major NIH grant application.

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# Abstract

Understanding of the pathophysiology of dystonia is critical to the development of new, principled, therapies. This, has however previously been limited by a lack of direct recordings from cortex and striatum simultaneously in unconstrained patients with dystonia. We now here have an extraordinary opportunity to investigate corticostriatal dystonia network pathophysiology through the use of next-generation devices that can deliver conventional deep brain stimulation therapy and also continuously record high quality signals from subcortical and cortical sites.

We plan to study oscillatory brain activity across the corticostriatal network in a cohort of implanted cervical dystonia patients using both sensory and motor assessments. Firstly, we will investigate sensory temporal discrimination and behaviorally relate this to oscillatory low frequency (LF) activity and surround inhibition. Next, we will correlate LF activity with dystonic motor symptoms in patients’ homes. Critically, we will then test the causal function of these signals using LF triggered adaptive DBS (LF aDBS). Finally, we plan a pilot clinical study of blinded LF aDBS compared to conventional stimulation.

This project will therefore provide crucial understanding on the network signaling underlying sensorimotor deficits in dystonia as well as piloting a new principled therapy that could improve efficacy and reduce side effects.

# Specific Aims

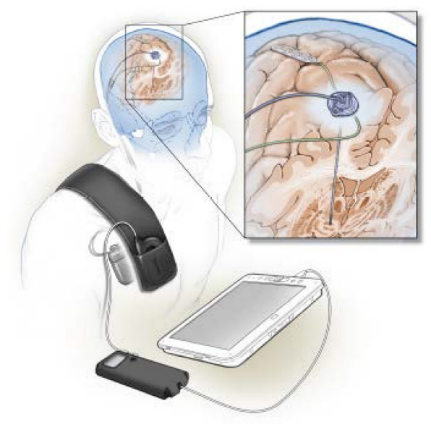
1. **Understand the network pathophysiology of dystonia**
   1. Here we will investigate the network wide pathophysiology of dystonia and investigate LF local field potential biomarkers of abnormal dystonic muscle activity during sensory and motor assessments.
2. **Testing causality of low frequency local field potential signals in dystonia**
   1. Having investigated correlative relationships of LF oscillatory activity with sensory and motor dystonic activity we will use temporally precise subcortical stimulation, targeted to LF signals, to investigate causal relationships.
3. **Pilot testing of clinical efficacy of adaptive Deep Brain Stimulation**
   1. Candidate biomarkers will then be put forward for clinical testing with (closed-loop) adaptive deep brain stimulation therapy (aDBS) with at home blinded testing of outcomes using AI derived video based kinematics.

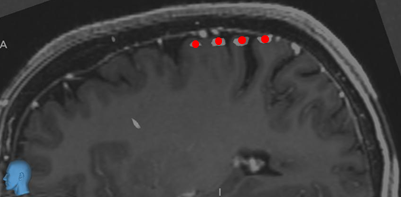
# Research Plan

## Rationale

Dystonia is a clinical disorder that presents with sustained or repetitive muscle contractions causing abnormal movements and / or postures1. Despite multiple and varied etiologies, this similarity of clinical presentations suggests a possible underlying unified pathophysiology at the network level. If understood, this raises the enticing prospect of new principled therapies that could treat or reverse a wide spectrum of dystonic conditions2.

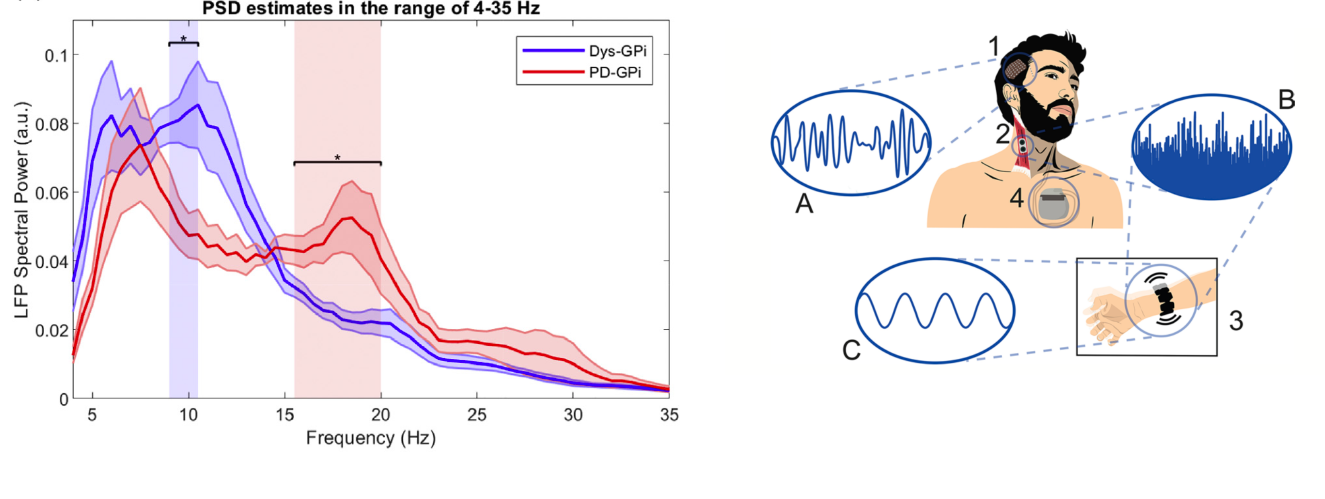
Although there has been significant progress in our understanding of the motor control deficits that are found in dystonia, our knowledge is still incomplete. A current prominent theory is that the underlying neurophysiology is related to abnormal activity in the corticostriatal circuit which may also extend to the cerebellar network3. At a functional level this manifests across a broad range of domains including abnormal sensory integration, plasticity changes and reduced intracortical / intrahemispheric inhibition4,5. The centrality of the basal ganglia in this pathophysiological network is supported by recording studies that show abnormal firing patterns in these structures5,6 and the clinical effectiveness of deep brain stimulation (DBS) of the subthalamic nucleus (STN) and the globus pallidus interna (GPi) in treating advanced dystonia7–9.

Despite, the identification of the key anatomical nodes in the network, much less is as yet known about how these nodes communicate with one other and particularly how this is perturbed in dystonia. Recently, attention has moved to signals which may index network dysfunction at the neuronal population level. These signals can be recorded during implantation of DBS and suggest a specific signal in the low frequency (LF; 3-11 Hz) range that relates to dystonia and is suppressed by therapeutic DBS 10,11. As yet, the causal and pathological significance of this signal plus whether it can be harnessed to improve DBS remains to be determined.

Recently, significant efforts have been put into designing new DBS systems for movement disorders that have the ability to *sense* and *stimulate* only when pathological neural activity appears. These systems are known as adaptive (or closed loop) deep brain stimulation (aDBS) and have been pioneered by the researchers associated with the current submission12. In Parkinson’s disease aDBS has been shown to have improved motor efficacy, less side effects and reduced battery life consumption compared to conventional therapy13,14. Our early studies launched the field of adaptive brain stimulation for movement disorders and are now progressing towards major, large scale clinical trials in Parkinson’s. Moreover, this work has inspired major development and investment from medical device manufacturers to create fully implantable DBS devices which have the ability to sense and stimulate (Fig 1).

Our team is now at the forefront of the implantation and use of these DBS devices (Fig 1) and a new, next generation investigational sense-and-stimulate device has recently been launched (SUMMIT RCS) which has the ability to stream unlimited amounts of cortical and subcortical data. In summer 2019 we implanted this new device into a patient with cervical dystonia, bilaterally into the STN and over the motor cortices (Fig1). This is the only dystonia patient in the world who is able to record high quality data from both the cortex and basal ganglia nodes of the corticostriatal circuit over prolonged periods and is already providing valuable insight into network physiology (see prelim. data; Fig 4-6).

**Fig 1. Bidirectional Sense and Stimulate DBS system.** System schematic (upper panel) with sagittal post op MRI showing ECOG (lower panel).

We propose therefore to expand this to a small cohort of (5) dystonia patients, implanted with the new RCS sense-and-stimulate device (bilaterally) in order to record from the whole cortico-striatal network during tasks that can reveal underlying pathophysiology, identify biomarkers and implement these to pilot aDBS for dystonia. We have previously discussed the neural signatures of dystonia and the potential for adaptive deep brain stimulation2,10. There are a number of potential biomarkers that could direct aDBS, including EMGs, wearable monitors and neural signals (Fig. 2). However, the most promising at present is the local field potential, recorded directly from the DBS electrode or electrocorticography (ECoG). Like Parkinson’s disease, dystonia appears characterized by abnormal oscillatory patterns of activity and synchronization10. Importantly, LFP LF activity, seems to correlate with dystonic EMG activity and clinical severity and has been found in both the STN and also the GPi6,15. Moreover, modulation of these signals has also been shown during the sensory trick maneuver (geste antagoniste) suggesting sensory input to, and gain control of this activity16. A critical finding has also been that these LF signals, both cortically and subcortically, are rapidly suppressed by therapeutic DBS11,17, suggesting a direct link to motor output and therapeutic benefit although causality has not yet been fully established. Therefore we propose that these LF signals may have a causal role in the motor control deficits as manifested in dystonia and represent a final common pathophysiological pathway that could be amenable to a new specific treatment with aDBS2.

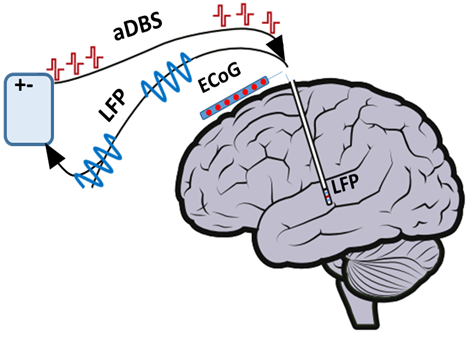
**Fig 2. Physiological biomarkers of Dystonia**. Schematic demonstrating the multiple different potential biomarkers that can be used to implement aDBS in dystonia. These include neural signals, electromyography and wearable sensors.

## Hypotheses

1. Local field potentials in the LF range (3-11 Hz) pathologically synchronize cortical and subcortical nodes and correlate with both motor and sensory deficits.
2. LF bursts play a causal role in the pathophysiology of sensorimotor integration abnormalities and surround inhibition deficits in dystonia.
3. Adaptive deep brain stimulation triggered off LF bursts has the potential to improve therapeutic efficacy and reduce stimulation related side effects by more directly targeting underlying pathophysiology.

## Relevance

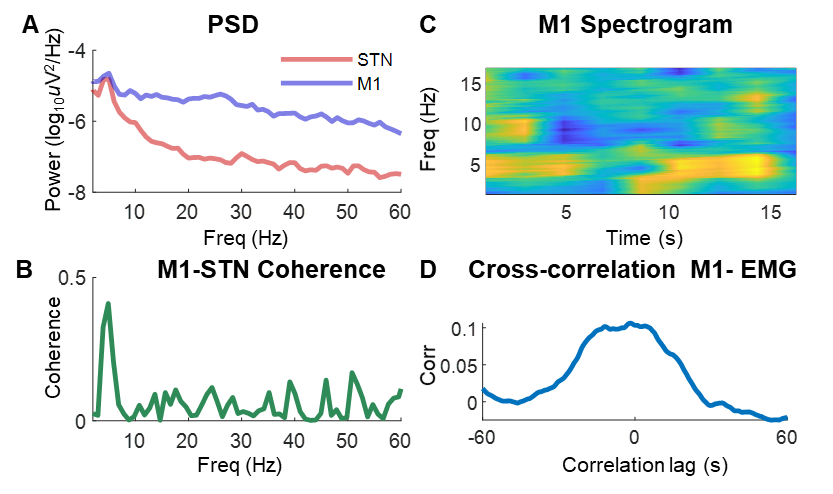
Although notable progress has thus far been made, our understanding of the pathophysiology of dystonia is still incomplete. This has limited the development of new therapies for this highly disabling disease. Current treatments for dystonia include medication, botulinum toxin therapy and for the more severe cases, DBS18. Although clinically beneficial, DBS still suffers from significant limitations19,20. Notably, treatment efficacy can be partial and accompanied by side effects when implanted at the GPi (bradykinesia) and STN (dyskinesia). Current shortcomings of DBS may be related to how it is now delivered in standard care, as a continuous train of high frequency pulses which will inevitably interfere with physiological as well as pathological activity.

Multiple converging lines of evidence suggests that dystonia should be considered as a network disorder and early compelling studies suggest that this network dysfunction may be mediated by LF oscillatory activity3. Therefore, if we could understand the pathophysiological significance of these brain rhythms in dystonia and harness them for personalized therapy it may be possible to advance a new stimulation treatment which could be significantly more efficacious and suffer from fewer side effects (Fig 3)2. Speculatively, it is also possible that by targeting underlying pathophysiological network activity directly it may prompt plastic changes that outlast the period of stimulation which could result in disease modification. Hence, this project proposes to dissect the pathophysiological role of LF oscillations in dystonia, link them to precisely defined sensorimotor deficits and leverage this understanding to test a new adaptive stimulation therapy which could help a wide range of dystonic patients.

**Fig 3. Schematic of aDBS for Dystonia**. Schematic demonstrating the adaptive control of DBS using subcortical LFPs or ECoG signals.

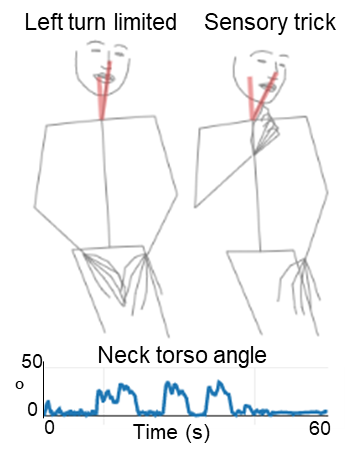
## Project Design and methods

**Participant recruitment:**

We have currently implanted 1 patient with cervical dystonia with bilateral STN DBS and sensorimotor cortical sensing electrodes and plan to recruit 4 more cervical dystonia patients by the end of this grant period. Inclusion criteria include: a diagnosis of cervical dystonia, confirmed by clinical observation by a Movement Disorders neurologist (IB) at University California, San Francisco (UCSF), male or female, and ages 18-80 years. Exclusion criteria include: secondary dystonia, marked dystonia affecting other regions than the cervical region, known structural brain abnormality and other major neurologic disorder. We plan to work with patients implanted in the STN as treatment with DBS at this nucleus is notably limited at present by stimulation induced dyskinesias21 which could be ameliorated by bursts of aDBS. Yet the STN offers the benefit of avoiding the potential of stimulation induced bradykinesia that has been observed in GPi DBS21. IRB approval has been obtained for the recording and aDBS component of the study with an amendment planned for the sensory task.

**Fig 4. Prelim data 1– Spectral features of corticostriatal network. A** Power spectral density of STN and M1 showing theta peak (patient 1). **B** Increased coherence between M1-STN at rest. **C** Spectrogram showing dynamic cortical theta activity, in bursts lasting a few < 5 s (color normalized between max and min). **D** Cross correlation of theta activity (3-6Hz) showing M1 correlating and just preceding the EMG.

**Phase 1 – Identify network related neural signatures of *sensory* and *motor* deficits in cervical dystonia**

LF oscillatory signals have previously be shown to be correlated with dystonic **motor activity**. However, this clinical correlation has not yet been systematically explored at both the cortex and basal ganglia simultaneously using high resolution (invasive) recordings or whilst looking at within subject fluctuations. Using the SUMMIT RCS sense-and-stimulate recording device, we can now record bilaterally from implanted cortical and basal ganglia electrodes, at high temporal and spatial resolution, continuously. This permits the studying of the oscillatory corticostriatal network in unprecedented detail. Using externally placed EMG sensors as well as accelerometers (ACC) that are built into the RCS device, we can now investigate how normal and abnormal movements correspond to underlying oscillatory network activity. We have found using data recorded in the laboratory that LF activity from the cortex and STN is strongly coherent at times and correlates with, and precedes, phasic oscillatory dystonic muscle activity seen at the neck muscles (See Fig 4. Prelim data 1).

*H1: We predict that repeated (high volume) home corticostriatal recordings will show a positive correlation between LF activity (total M1 & STN power, coherence) and cervical dystonic severity.*

Cervical dystonia is currently assessed through clinical rating by a neurologist using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTR). This scale is highly clinical valuable, however, it suffers from limitations in our context, namely, the subjective nature of the scale, the difficulty in performing it repeatedly at home and inter/intra-rater reliability. We have partnered with a collaborator ([www.machinemedicine.com](http://www.machinemedicine.com); Dr Jonathan O’Keefe CEO) that uses artificial intelligence and advanced computer vision software to extract human kinematics from recorded videos (<https://www.dropbox.com/s/isrr94f6tfjeuyp/MM_SensoryTrick.wmv?dl=0> for video; Fig 5). This will enable the rapid and reliable assessment of head movement kinematics both in the laboratory and at home for correlation with LF oscillations as recorded through the SUMMIT RCS.

In addition to showing a correlation of LF with dystonic severity we want to investigate how LF activity contributes to the pathophysiology of dystonia through impaired **sensory functioning**. Sensory abnormalities, including those related to temporal aspects of sensory function, have been demonstrated in multiple forms of dystonia and have been postulated to be central to its pathophysiology22. We therefore plan to investigate the neural signaling of sensory functioning whilst performing a behavioral paradigm that has previously been shown to be abnormal in cervical dystonia23. Somatosensory temporal discrimination (STD) permits the investigation of somatosensory function in dystonia but also, through the analyses of somatosensory evoked potentials, an investigation of intracortical, corticostriatal and interhemispheric inhibition.

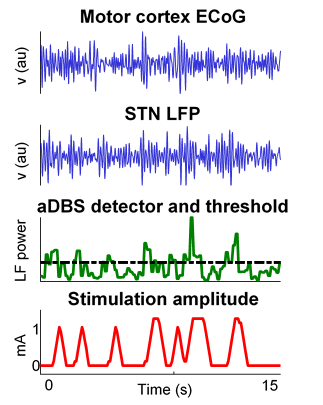
**Fig 5. Prelim data 2 - AI based video kinematics.** Patient 1 has right CD with limited left neck movement, improved with sensory trick. Neck torso angle is shown (lower panel) during x3 repeats.

*H2: We predict that STD will be inferior during periods of increased LF activity. We also predict that network inhibition (corticostriatal, intracortical and intrahemispheric) will be decreased during LF activity as shown by an increased size of somatosensory evoked potentials at these sites during bursts of LF activity.*

**Phase 2 – Demonstrate a casual role of LF activity in dystonic pathophysiology with LF triggered aDBS**

Having established a correlative relationship between LF activity, motor activity, clinical severity and sensory pathophysiology we next intend to demonstrate that this signal plays a causal role and is not simply epiphenomenal or re-afferent activity. In order to do this we will use precisely timed bursts of subcortical stimulation, locked to LF activity during our behavioral tasks and muscular assessment with EMG and ACC (Fig 6). The causal nature will be shown by the fact that we can reverse the correlative deficits demonstrated in Phase 1 in a precise manner that is linked to LF oscillations.

*H3: We predict that stimulation that is locked to bursts of LF activity will result in improved dystonic motor output (reduced clinical severity) and improved STD compared to asynchronous aDBS*

****An important confound to rule out in this experiment is that intermittent stimulation is itself the cause of the improvement in motor and sensory function. Fortuitously, with the use of the RCS and threshold crossing based aDBS set up (Fig 6), we have an ideal potential internal control and can rule out this confound by reversing the algorithm guiding aDBS activation. We will initially construct the control algorithm to rapidly increase stimulation during a LF burst and evaluate for improvement in CD severity. We will subsequently reverse this contingency so that stimulation is delivered only when LF drops below the same threshold. If LF oscillations are causal to motor sensory dysfunction in dystonia then we predict that stimulation would cause significantly more improvement in dystonic muscle activity and STD when delivered synchronously, as opposed to asynchronously, to LF bursts.

**Phase 3 – We predict that chronic stimulation with LF based aDBS at the STN will be more effective than conventional stimulation and reduce side effects**

STN DBS is limited by partial efficacy and side effects, particularly dyskinesia19,20. We predict that if LF activity is indeed causal to dystonic pathophysiology, then stimulation using LF aDBS should be more efficacious than conventional continuous DBS therapy. Moreover, by stimulating intermittently in a temporally targeted manner, it may be possible to increase the peak level of stimulation without inducing dyskinesias.

We therefore propose to optimize LF aDBS in clinic and then test patients at home in a blinded fashion using automated (Machine Medicine) based video rating of the cervical dystonic neck movements. This will take the form of within subject, repeated measures, N-of-1 testing whereby each subject will be placed on cDBS versus aDBS on multiple blinded counterbalanced days.

*H4: We predict that LF aDBS will result in better motor outcomes than cDBS and through intermittent targeted stimulation, prevent dyskinesias.*

## Data analysis plan

Phase 1: **Motor & sensory** correlations with LF signals. We will record corticostriatal LFPs concurrent with motor kinematics. We will use wavelet transformations to extract continuous estimates of LFP amplitudes in different frequency ranges and for evoked responses we will use event locked LFP averaging. Theta burst definition and analysis will be carried out using machine learning (Hidden Markov Modelling24). Functional connectivity between cortex and STN will be analyzed by coherence and granger causality. Statistical analyses with sensory and motor state will be carried out using Pearsons correlations.

**Fig 6. Prelim data 3- trial of LF aDBS for Dystonia in first dystonic patient**. A brief (15s) segment of cortical and subcortical activity (blue), smoothed LF power (green) with threshold (black) and ramped aDBS (up to 1.2mA). Data shown for left side.

Phase 2 & 3: Testing causality and aDBS at home: Here we will repeat the behavioral paradigms outlined above but perform a within subjects contrast of synchronous versus asynchronous LF aDBS by t-testing. We will then use linear mixed modelling to combine the data across all subjects (including the within subject individual events). All data (Phase 1-3) will be tested for normality and if non-gaussian, non-parametric tests will be employed. Appropriate multiple comparison correction using the false discovery rate will also be used.

Power analysis: We have completed a power analysis for the clinical testing (phase 3) component of the study. These will take the form of multiple N-of-1 studies completed over pairs of stimulation days and therefore sample size here refers to paired days (not subjects which is fixed at 5). aDBS has not previously been tested in dystonia and therefore estimates of effects size are highly speculative. However, we have looked at previously effect sizes of aDBS in movement disorders (Parkinson’s disease) and used an effect size which is half as large (15% improvement of aDBS over cDBS) and the same standard deviation of 15% (also conservative as this is now a within subject N of 1 study, rather than across subject study). We consider a 15% improvement to be at threshold for a clinically meaningful result. This predicts that we would detect a significant result with a power of 95% with 16 pairs of days per subject (aDBS versus cDBS). Total (32 days).

## Milestones

The three phases will be staggered (but overlapped in different patients) over the 2 year grant period. We expect to start the process of applying for RO1 funding and write up of results in the final 6 months of the 2yr grant period.

## Pitfalls

Patient recruitment: As the busiest DBS centre on the west coast we believe that the implantation of 4 further cervical dystonia patients over the next 2.5 years is entirely realistic. To mitigate reduced recruitment possibilities, we would potentially expand the inclusion criteria to include generalized dystonia patients. Additionally, we have as a collaborator, Dr Martijn Beudel, a movement disorders expert in the Netherlands who is studying dystonia patients in Amsterdam with GPi implantation giving the potential to expand enrolment of the Phase 1 (neurophysiology) component to the Netherlands.

Small patient cohort: Although the patient numbers are relatively low, we feel that this is appropriate for a pilot study pending larger scale NIH funding for a formal clinical trial. Moreover, the large volumes of data per subject will permit N of 1 analyses within individual subjects and these will be combined using linear mixed models to optimize statistical efficiency and allow (cautious) group level inferences to be made.

Biomarkers: Although LF signals are promising as a candidate biomarker of pathophysiology in dystonia, it may turn out that they are epiphenomenal, or only related to a component of the dystonic activity (phasic component). In such a scenario, it may still be possible to use LF signals as a biomarker to control aDBS to clinical benefit. However, from our pilot studies in patient 1 (data not shown) we already have a secondary biomarker of interest (STN gamma) that appears to index stimulation induced dyskinesias and would shift our phase 3 investigation to this alternate biomarker should LF based aDBS fail.

Machine medicine: This is an exciting startup company with significant seed funding to enable growth and expansion. However, as part of our contract with them, we have agreed a “sunset clause” such that, should the company not continue we would be able to retrieve all old data. At this stage we would modify our plans to use traditional externally place EMG and ACC sensors in the laboratory.

## Publications

Anticipated timeframe for manuscript submission is summer 2021 and would potentially include journals of clinical neurology and movement disorders as well as neuroscience or neurophysiology journals.

## Patents

Patents, inventions and registration of intellectual property rights will be processed through the UCSF Office of Technology Management as per University of California guidelines and policy as agreed between the Dystonia Medical Research foundation and the University of California.

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# Lay Summary

Dystonia is a highly challenging condition which is characterized by contraction (pulling) of muscles against each other, outside of voluntary control. This leads to abnormal positions and movements of different parts of the body which can be very painful and disabling. There are some available treatments for dystonia including drugs, injections into the muscles to weaken them or for the most severe symptoms, a brain operation which implants pacemaker wires into the movement centers of the brain called deep brain stimulation (DBS). However, all these treatments have limitations including the fact that they only result in partial benefit for symptoms and all cause side effects which can be very unsatisfactory for people living with dystonia.

If we understood the underlying cause of dystonia better we should be able to design treatments that are more effective. We have learnt a lot already, specifically, that although the symptoms result in problematic contractions of the muscles, the underlying problem actually starts in the brain. There are many different causes of dystonia but many result in similar patterns of muscle activation. It is thought therefore that there might be a process that is common to many of these underlying illnesses, specifically in how the brain functions and communicates. Recent work has shown that the brain signals in dystonia are different from those in healthy people or with other neurological illnesses. It has also been shown that there is not one single area of the brain which appears to be the problem but rather abnormalities in how many different areas of the brain communicate with each other. We are starting to understand how this abnormal signaling between areas of the brain might occur and importantly, that it involves changes not only in how often particular brain regions activate but also the pattern of firing.

The DBS operation not only works as a therapy but also is helping us to understand how the brain communicates in disease by enabling us to record from the brain through the pacemaker wires. This has revealed a pattern of activity in the deep parts of the brain that repeats around five times per second in people with dystonia and is linked to muscle activity. However, we don’t yet know the significance of this signal and whether it is *causing* the muscles to contract or is *simply a marker that they have done so*. Also, if it is a cause of dystonia, it isn’t yet known how this interferes with the healthy sensory messages that come into the brain or the movement signals that leave the brain.

To answer these questions, we plan to use a new research DBS (“brain radio”) device which has advanced capabilities, in that it can stimulate (and give standard DBS therapy), but it can also listen (record) brain signals from the deep and surface parts of the brain together. We have already implanted this device in one person with neck dystonia and found that we can accurately record the 5 per sec brain signal and that communication using this channel between the deep and surface parts of the brain appears increased. Next we plan to implant the brain radio in four further participants with dystonia and study the brain signals during experiments that measure sensation and muscle movements. By recording extensively while the participants are at home, we plan to show that the 5 per sec signal is larger when the dystonia is more severe. To measure this we will use artificial intelligence (AI) computer systems that are trained to analyze videos of movements. Additionally we hope to show that the 5 per sec signal interferes with the brains ability to detect sensation.

If we can demonstrate that the 5 per sec signal is related to both sensation and movement, we next want to show that that may actually be causing the abnormal movements. To do this we plan to give bursts of brain stimulation, only when the 5 per sec signal is present and compare this to bursts of stimulation when its not present. We hope that this will show that the signal is indeed partially causing the muscle contraction problem. In the last part of the study we will test this new type of targeted stimulation for longer periods in the participants homes to see if it can be a useful treatment which is more effective and causes fewer side effects than standard continuous DBS.

We believe that this study will be very helpful in furthering our understanding of how brain signaling goes wrong in dystonia, knowledge which could potentially allow us to design new and significantly improved therapies for people living with dystonia.

2019 Clinical and Basic Aspects of Dystonia RFA

# Grant Application Budget Form

**Budget:** *Itemize requested budget. Amount requested must not exceed $80,000 per year. Refer to the Research Funding Terms and Conditions for a list of unallowable costs.*

|  |  |  |  |
| --- | --- | --- | --- |
| **Item** | **Year 1** | **Year 2** | **Total** |

|  |  |  |  |
| --- | --- | --- | --- |
| ***Personnel***  **Simon Little, PhD**  **Ian Bledsoe, MD**  **Philip Starr, MD, PhD** | **$62,126**  **$11,699**  **$5,150** | **$62,090**  **$11,713**  **$5,156** | **$124,216**  **$23,412**  **$10,306** |
| ***Supplies*** |  |  |  |
| ***Equipment*** |  |  |  |
| ***Other Expenses***  **UCSF Data Network**  **UCSF CCDSS**  **UCSF GAEL** | **$226**  **$303**  **$496** | **$226**  **$303**  **$512** | **$452**  **$606**  **$1,008** |
| **Total** | **$80,000** | **$80,000** | **$160,000** |

2019 Clinical and Basic Aspects of Dystonia RFA

Grant Application Budget Form

**Budget Justification:** *Provide justification for major budget items*

**Simon Little, PhD, Principal Investigator** (37% effort, salary and benefits requested) As PI, Dr. Little will be responsible for the overall management of the project including study design, experiment completion, analysis and write up of results and application for further NIH funding.

**Ian Bledsoe, MD, Co-Investigator** (5% effort, salary and benefits requested) Dr. Bledsoe is an expert in the clinical phenomenology of dystonia and as such will be involved in study recruitment and patient assessment during aDBS (in addition to the automated machine learning component of dystonia).

**Philip Starr, MD, PhD, Co-Investigator** (1% effort, salary and benefits requested) Professor Starr will be responsible for the neurosurgical monitoring of patients and scientific supervision of the electrophysiology and aDBS components of the study.

**Current Research Support:** *Provide project title, funding agency, funding period and amount of* ***all*** *of your**active and pending research support. Explain any potential overlap with this application.*

Dr Little has only recently moved from the UK to UCSF (April 2019) and is currently supported by departmental salary and has no external grant support.

**Available Resources:** *Provide a description of facilities and resources available for this project.*

The department of neurology and neurosurgery, where this research will be carried out, are internationally respected research centers and well equipped for translational neurophysiological studies. Specifically there is dedicated laboratory space for research patients during investigational assessments in addition to dedicated office space for all research personnel with state of the art computing and IT support.

Through a previous, large scale project using the Medtronic Summit RCS in Parkinson’s patients, there is a well-developed research platform for the implementation of data streaming with the RCS device as well as a customized software interface to facilitate the safe and reliable programming of adaptive deep brain stimulation. Professor Starr has also employed a full time software engineer as well as senior post doctoral students from an engineering background to ensure technical efficiency and safety. The project is also supported by readily available technical input from the Medtronic engineering team. The previous project with Parkinson’s has resulted in the technical challenges of using a new complex device already having been solved so that these gains will be built upon with this current dystonia project. Notably, as per our Parkinson’s protocol, the cost for the neurosurgical implantation of the device will be covered by insurance (as DBS would be part of standard clinical care). Additionally, the RCS SUMMIT device itself is donated from Medtronic in order to support neurophysiological research meaning that the overall cost of this study is very low when the actual value in terms of additional resources that it would leverage is considered.

# Biographical Sketches

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

**BIOGRAPHICAL SKETCH**

**Provide the following information for the Senior/key personnel and other significant contributors.**

**Follow this format for each person. DO NOT EXCEED FIVE PAGES**.

NAME: Simon James Little

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Assistant Adjunct Professor

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

| INSTITUTION AND LOCATION | DEGREE  (if applicable) | Completion Date  MM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| Cambridge University | First Class Honours | 01/1999 | MVST1a |
| Cambridge University | First Class Honours | 01/2000 | MVST1b |
| Cambridge University | First Class Honours | 01/2001 | BA Experimental Psychology |
| University College London | Distinction | 01/2004 | MBBS - Clinical Training |
| Royal College of Physicians | 92% | 01/2008 | MRCP |
| Oxford University | Awarded 2014 | 01/2014 | DPHIL (PHD)  Experimental Neurology |
| Royal College of Physicians | 76% | 01/2016 | Neurology Speciality Certificate |
| Middlesex University - Minster centre for Integrative Psychotherapy Training | Certificate | 01/2016 | Foundational Training |

**A. Personal Statement**

This project proposal integrates my expertise in neurophysiology, adaptive deep brain stimulation and advanced modelling and therefore I have shown that I have the requisite skills to undertake it and complete the proposed research successfully. I have been developing the ideas central to this project over the last two years and so am very excited about it and motivated to ensure its success. Importantly, I am also supported by highly respected international collaborators and UCSF mentors to provide any necessary guidance. I have a strong proven track record in clinical academia having previously obtained highly competitive personal grant funding on three occasions. Through these grants, which I have personally administered, I have shown on each occasion that I am able to tackle highly challenging and complex research questions which are multidisciplinary, encompassing direct patient care, neurophysiology, behavioural assessments and bio-engineering.

Consequently, these research efforts have on multiple occasions led to significant advances. I demonstrated the first in man proof-of-principle that deep brain stimulation for Parkinson’s can be successfully controlled online, in real time, using population signals recorded from the local field potential (LFP) to improve efficacy and reduce side effects. This has created a new field of translational neuroscience, significant industry investment and technological development and the progression to large scale international trials which are commencing shortly. Subsequently, I also investigated cortical signals of movement in healthy subjects using a different technique – Magnetoencephalography (MEG). Through this work I was able to show that cortical beta movement signals are highly dynamic bursts, focal and relate to movement initiation and errors. This challenges very long standing concepts in motor neuroscience regarding the nature of cortical movement signals and heralds the possibility of new targets for adaptive brain stimulation. These efforts have given me the technical and analytical skills necessary to complete the proposed project here outlined, but moreover, have also clearly demonstrated the importance of communication skills, leadership, administrative skills and attention to detail in ensuring success. If awarded, I will bring all these skills to bear on this project.

**B. Positions and Honors**

Positions and Employment

|  |  |
| --- | --- |
| 2004-2005 | House Officer, General Medicine, Whittington Hospital NHS Trust |
| 2005-2005 | House Officer, General Surgery, Royal Cornwall Hospitals NHS Trust |
| 2005-2007 | Foundation Trainee, General Medicine, St Thomas's Hospital NHS Trust |
| 2007-2009 | Core medicine and neurology training, Neurology & Neurosurgery, Kings College Hospital |
| 2009-2011 | Specialist Registrar Neurology, Neurology, St Georges Hospital NHS Trust |
| 2011-2014 | PHD, Experimental Neurology, Oxford University |
| 2014-2015 | Specialist Registrar Neurology, Neurology, St Georges Hospital NHS Trust |
| 2015-2017 | Specialist Registrar & Clinical Lecturer, Neurology, National Hospital of Neurology, London |
| 2017-2019 | Senior Clinical Researcher, Department of Clinical and Motor Neuroscience, UCL, London |
| 2017-2019  2019-2019 | Consultant (Attending) Neurologist, Neurology, Homerton University NHS Foundation Trust  Assitant professor neurology, University California San Francisco |
|  |  |

Other Experience and Professional Memberships

|  |  |
| --- | --- |
| 2008-2019 | Royal College of Physicians - Member (Examination passed 2008) |
| 2011-2012 | Advisor on Activa PC&S development, Medtronic |
| 2011-2019 | Internal Reviewer, University College London. Research and Development. Internal reviewer. |
| 2011-2019 | Association of British Neurologists - Member |
| 2016-2016 | External Reviewer, Parkinson's Disease UK. |
| 2017-2019 | British Medical Association - Member |
| 2018-2018 | External Reviewer, Swiss National Science Foundation. |
| 2019-2019 | Movement Disorders Society |

Honors

|  |  |
| --- | --- |
| 2000 | Tancred Medical Scholarship, Cambridge University |
| 2001 | BA Scholarship, Christ's College Cambridge |
| 2001 | Certificate of Merit, University College London |
| 2002 | Certificate of Merit, University College London |
| 2003 | Distinction in Neurology & Psychiatry, University College London |
| 2003 | Howard Murray Neurology Prize, University College London |
| 2003 | Crick, Constantine & Anderson Prize. Obstetrics & Gyanaecology, University College London |
| 2004 | Atchinson prize for overall performance in medical finals, University College London |
| 2011 | Wellcome Trust - Clinical Research Training Award, Wellcome Trust |
| 2014 | Rosetrees Trust Award, Oxford University |
| 2014 | Wellcome Trust - Clinical Research Career Development Award - Stage 1, UCL, London |

**C. Contribution to Science**

1. Identifying spectral biomarkers of parkinsonism for adaptive brain stimulation

My research has focused on exploring the cortico-striatal signals of movement in health and disease and leveraging these to design translational brain stimulation therapies. For my PhD I received a Wellcome trust training fellowship to support my research and showed that subcortical local field potential signals in the beta range (13 – 30 Hz) index slowness and stiffness in Parkinson’s disease. Through causal stimulation interventions I also found evidence that these signals appear to be pathological. I then used advanced online filtering and control systems to demonstrate the first demonstration in humans that these signals can be used to control delivery of deep brain stimulation in a principled manner requiring <50% of the electrical energy but producing improved motor efficacy compared to best conventional therapy. This was published in the Annals of Neurology (2013) and opened up a new field of translational research of adaptive deep brain stimulation (aDBS) for movement disorders (>500 citations).

a) **Little, S**., Pogosyan, A., Kuhn, A.A., and Brown, P. (2012). Beta band stability over time correlates with Parkinsonian rigidity and bradykinesia. Exp. Neurol. 236, 383–388.

b) **Little, S.**, Joundi, R.A., Tan, H., Pogosyan, A., Forrow, B., Joint, C., Green, A., Aziz, T.Z., and Brown, P. (2012). A torque-based method demonstrates increased rigidity in Parkinson’s disease during low-frequency stimulation. Exp. Brain Res. 219, 499–506.

c) **Little, S.**, and Brown, P. (2014). Focusing Brain Therapeutic Interventions in Space and Time for Parkinson’s Disease. Curr. Biol. 24, R898-909.

d) **Little, S.**, Pogosyan, A., Neal, S., Zavala, B., Zrinzo, L., Hariz, M., Foltynie, T., Limousin, P., Ashkan, K., Fitzgerald, J., et al. (2013). Adaptive deep brain stimulation in advanced Parkinson disease. Ann. Neurol. 74, 449–457.

2. Clinical translation of adaptive stimulation therapy – improving efficacy and reducing side effects

Next I sought to validate aDBS for sustained periods of stimulation while quantifying axial symptoms and measure the impact of aDBS on stimulation induced side effects aiming to transition to clinical therapy. I found that aDBS was effective when delivered bilaterally and that the two hemispheres were functionally uncoupled, that aDBS appropriately tracked medication state and also reduced side-effects including speech deterioration. Furthermore, we used our aDBS paradigm to demonstrate the critical temporal window for causing impulsivity and identify the role of prolonged beta bursts in the pathophysiology of Parkinson’s disease. Finally, we used this approach to identify spectral biomarkers of tremor disorders and test aDBS for tremor as well as dystonia.

a) **Little, S.**, Tan, H., Anzak, A., Pogosyan, A., Kühn, A., and Brown, P. (2013). Bilateral functional connectivity of the basal ganglia in patients with Parkinson’s disease and its modulation by dopaminergic treatment. PLoS One 8.

b) **Little, S.**, Beudel, M., Zrinzo, L., Foltynie, T., Limousin, P., Hariz, M., Neal, S., Cheeran, B., Cagnan, H., Gratwicke, J., et al. (2015). Bilateral adaptive deep brain stimulation is effective in Parkinson’s disease. J. Neurol. Neurosurg. Psychiatry 87, jnnp-2015-310972.

c) **Little, S.**, Tripoliti, E., Beudel, M., Pogosyan, A., Cagnan, H., Herz, D., Bestmann, S., Aziz, T., Cheeran, B., Zrinzo, L., et al. (2016). Adaptive deep brain stimulation for Parkinson’s disease demonstrates reduced speech side effects compared to conventional stimulation in the acute setting. J. Neurol. Neurosurg. Psychiatry 87, 1388–1389.

d) Tinkhauser G, Pogosyan A, **Little S**, Beudel M, Herz D, Tan H & Brown, P. (2017). The modulatory effect of adaptive deep brain stimulation on beta bursts in Parkinson’s disease. Brain; 140(4), 1053–1067.

3. Understanding cortical movement signalling using precision MEG and translational implementations in movement disorders

Having identified subcortical signalling of pathological movement I next looked to investigate the cortical component of the human motor network. I was awarded a further Wellcome trust grant to support this and investigated motor cortical beta oscillations, their dynamic properties and computational functional role using advanced high precision Magnetoencephalography and EEG in patient populations. Firstly I evaluated a personalised 3D printed headcast methodology for optimising MEG source inversion accuracy using Hidden Markov Models (HMM). Having validated high spatio-temporal resolution head-cast MEG, I next used this technique to dissect cortical motor signalling in healthy subjects. I showed that cortical beta is formed of rapid bursts which are spatially focal, unilateral and delay movement onset and index movement errors. Following the discovery of beta bursting in normal subjects, I investigated motor cortical spectral dynamics across a range of disease states. Again using machine learning, we found that cortical beta bursts may be abnormal in Parkinson’s patients at movement initiation (in submission) and that beta may provide a diagnostic biomarker in psychogenic functional movement disorders. At UCSF we are now testing cortical beta bursting as a biomarker of adaptive DBS.

a) **Little, S.**, Bonaiuto, J., Barnes, G., and Bestmann, S. (2019). Human motor cortical beta bursts relate to movement planning and response errors. Plos Biology Oct 4;17(10):e3000479.

b) **Little, S.**, Bonaiuto, J., Meyer, S.S., Lopez, J., Bestmann, S., and Barnes, G. (2018). Quantifying the performance of MEG source reconstruction using resting state data. Neuroimage 181, 453–460.

c) **Little S** & Bestmann, S. (2015). Computational neurostimulation for Parkinson’s disease. Progress in Brain Research; v222, 163–190.

d) Teodoro, T., Meppelink, A.M., **Little, S.**, Grant, R., Nielsen, G., Macerollo, A., Pareés, I., and Edwards, M.J. (2018). Abnormal beta power is a hallmark of explicit movement control in functional movement disorders. Neurology 90, e247–e243.

4. Future work - investigating the neural architecture of dystonia for aDBS

I have now gained extensive experience in both invasive and non-invasive neuroimaging, computational modelling, adaptive neurostimulation and clinical trial design. I have moved to UCSF to integrate these aspects together into a research platform to develop personalized adaptive therapies for neurological disorders. I am working to test aDBS in advanced, fully implantable, sense-and-stimulate DBS devices that UCSF is a world leader in utilizing. I plan to now translate my previous experiences in Parkinson’s disease to a new condition – namely dystonia. Along with my international collaborator Dr Beudel, we have been working and laying the groundwork for aDBS in dystonia for the last 3 years and I have assisted Dr Beudel in the Netherlands in piloting aDBS off low frequency activity using externalize leads during DBS battery change. The project proposed herein is the first to perform this using fully implantable devices and embedded algorithms. Additionally, it is the first attempt to implement this in the STN nucleus, where aDBS may arguably be of more benefit due to the presence of stimulation induced dyskinesias. The theoretical underpinnings of this approach that we have been planning are included in the following publications.

a) Beudel, M., Cagnan, H. & **Little, S**. Adaptive Brain Stimulation for Movement Disorders. (2018) Prog. Neurol. Surg. 33, 230–242.

b) Piña-Fuentes, D, Beudel, M, **Little, S**. et al. The characteristics of pallidal low-frequency and beta bursts could help implementing adaptive brain stimulation in the parkinsonian and dystonic internal globus pallidus. (2019) Neurobiol. Dis. 121, 47–57.

c) Piña-Fuentes, D, van Zijl, J., Van Dijk J, **Little, S.**, et al. Toward adaptive deep brain stimulation for dystonia. (2018). Neurosurg. Focus 45, E3

Complete List of Published Work in MyBibliography:

<https://www.ncbi.nlm.nih.gov/myncbi/1Zi1fqvcyg2ANg/bibliography/public/>

**D Research Support**

On-going Research Support

|  |
| --- |
| Having just moved to UCSF in April 2019 from the UK I do not as yet have personal grant support. My salary is currently supported by the Department of Movement Disorders and Neuromodulation. After gathering pilot data as outlined in this grant application I plan to apply for my own RO1 funding at the end of the grant period. As such, this grant would be critical to my ongoing research career and to advancing the study of the network neurophysiology of movement disorders and the translation to new treatments. The overall goal of the study is too show the precise, quantitative, behavioral effects of low frequency oscillations in dystonia and stimulation subcortically. This has the potential to greatly advance from the correlative neurophysiological studies that are currently performed. I will supervise the project, particularly the data analysis components and preparation of a new grant application to the NIH using the pilot data. Dr Bledsoe will be responsible to patient selection and the sensory discrimination component of the study. As this is my first grant application in the US and I am currently supported by general funds, this does not significantly overlap with other projects. This will lead to a future major grant application for NIH funding. |

Completed Research Support

|  |
| --- |
| 105804/Z/14/Z Little (PI) 02/01/15-02/01/19  Wellcome Trust An investigation into the neurocomputational role of brain oscillations in human motor control for health and disease  This was a personal fellowship award to myself to cover 3 years of post - doctoral research (with 1 year of integrated neurology training) investigating cortical signals of movement control.  Role: Lead Applicant - -£411,430  Little (PI) 02/01/14-08/01/14  Rosetrees Trust Advancing Adaptive Deep Brain Stimulation for Parkinson's Disease  A brief (6 months) follow on grant following my PHD to extend and continue my work on adaptive deep brain stimulation.  Role: Lead Applicant - £21,500  093929/Z/10/Z Little (PI) 02/01/11-02/01/14  Wellcome Trust An investigation into the neurophysiological biomarkers of Parkinson’s disease in closed loop deep brain stimulation.  A personal clinical research training fellowship to cover my PHD investigating subcortical biomarkers of movement control.  Role: Lead Applicant - £172,786 |

OMB No. 0925-0001 and 0925-0002 (Rev. 01/18 Approved Through 03/31/2020)

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Starr, Philip A

eRA COMMONS USER NAME (credential, e.g., agency login): starrp

POSITION TITLE: Professor in-Residence of Neurological Surgery

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

| INSTITUTION AND LOCATION | DEGREE  (if applicable) | Completion Date  MM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| Princeton University, Princeton, NJ | B.A. | 05/83 | Chemistry |
| Harvard Medical School, Boston, MA | M.D. | 05/89 | Medicine |
| Harvard Medical School, Boston, MA | Ph.D. | 05/89 | Neurobiology |
| Brigham and Women’s Hospital, Boston, MA | Internship | 1989 -1990 | General Surgery |
| Brigham and Women’s Hospital and Children’s Hospital, Boston, MA | Residency | 1990 - 1996 | Neurosurgery |
| Emory University, Atlanta, GA | Fellowship | 1996 - 1998 | Movement Disorders Surgery and physiology |

1. **Personal Statement**

I am surgical director of the most active program for deep brain stimulation (DBS) implantation surgery in the Western USA, and have implanted devices into over 1800 patients with movement disorders, pain and related conditions. I direct a laboratory focused on cortex-basal ganglia networks in humans, and mechanisms of therapeutic DBS for movement disorders, utilizing multisite physiological recording in humans undergoing neurosurgery (1-2). Since 2013, I have been implanting investigational neural interfaces that combine a sensing capability with neurostimulation, into humans undergoing DBS (3-4).

I will fully support Dr. Simon Little in this Dystonia Foundation “Basic and Clinical aspects of Dystonia”. The study “A next generation sensing neural interface study for adaptive DBS in dystonia” requires extensive technical and regulatory infrastructure, for the use of implantable neural interfaces that sense, store, and wirelessly transmit neural signals. My laboratory and clinical group is one of very few in the world with the expertise to carry out the proposed studies. The proposed studies are likely to illuminate the underlying pathophysiological basis of population based signals for dystonia and has the potential to advance a new treatment for the condition, namely adaptive deep brain stimulation.

1. de Hemptinne C, Swann NC, Ostrem JL, Ryapolova-Webb ES, San Luciano M, Galifianakis NB, Starr PA. Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease. ***Nature Neuroscience*** 18(5):779-86, 2015. PMCID: PMC4414895.
2. Crowell AL, Ryapolova-Webb ES, Ostrem JL, Galifianakis NB, Shimamoto S, Lim DA, Starr PA. Oscillations in sensorimotor cortex in movement disorders: an electrocorticography study. ***Brain***,135 (Pt 2):615-30, 2012. PMCID: PMC3281473.
3. Swann, N.C., C. de Hemptinne, S. Miocinovic, S. Qasim, S.S. Wang, N. Ziman, J.L. Ostrem, M. San Luciano, N.B. Galifianakis, and Starr P.A, Gamma Oscillations in the Hyperkinetic State Detected with Chronic Human Brain Recordings in Parkinson's Disease. ***J Neurosci***, 2016. 36(24): p. 6445-58. PMCID: PMC5015781.
4. Swann NC dHC, Thompson MC, Miocinovic S, Miller AM, Gilron R, Ostrem JL, Chizeck H and Starr PA. . Adaptive deep brain stimulation for Parkinson’s disease using motor cortex sensing. **J Neural Eng** 15(4):046006, 2018. PMCID: PMC6021210

**B. Positions and Honors**

Positions and Employment

1998 - 2003 Assistant Professor of Neurosurgery, University of California, San Francisco

2003 - 2009 Associate Professor of Neurosurgery, University of California, San Francisco

2001 - 2010 Surgical Director, Parkinson’s Disease Research, Education and Care Center (PADRECC) at San Francisco Veteran’s Affairs Medical Center

2006 - present Dolores Cakebread Endowed Chair in Neurological Surgery

2009 - present Professor of Neurosurgery, University of California, San Francisco

2011 - present Director of Functional Neurosurgery, University of California, San Francisco

2014 – present Graduate program in Neuroscience, UCSF

Other Experience and Professional Memberships

*Professional Memberships*

1997 - American Association of Neurological Surgeons

1998 - Society for Movement Disorders

2000 - American Society for Stereotactic and Functional Neurosurgery

2007 - International Basal Ganglia Society

2007 - American Academy of Neurological Surgeons

2009 - Society for Neuroscience

*NIH Study section*

2011-2017 NIH study section regular member, Clinical Neurosciences and Neurodegeneration (CNN)

2016 ZNS1 SRB-J Udall Center Review

*Editorial review*

2006-2010 Editorial review board, *Stereotactic and Functional Neurosurgery*

2000-present Ad hoc reviewer for: *Neurosurgery, Neurology, Pain, Neuromodulation, Brain Research, Experimental Neurology, Movement Disorders*, *Journal of Neurology, Neurosurgery, and Psychiatry, European Journal of Neuroscience, Journal of Neurophysiology, Brain*, *New England Journal of Medicine*, *Journal of Neuroscience, Annals of Neurology*, *Cerebral Cortex, Frontiers in Human Neuroscience, Journal of Neuroscience, Nature Reviews Neuroscience*

*Patents*

*2016* US patent # 9,295,838*.* Methods and systems for treating neurological movement disorders

*Service to Professional Organizations*

2004 Scientific program director, Biennial Meeting of the American Society for Stereotactic and Functional Neurosurgery, Cleveland, Ohio

2004 - 2006 Secretary-Treasurer, American Association for Stereotactic and Functional Neurosurgery

2006 - 2008 Vice President, American Association for Stereotactic and Functional Neurosurgery

2008 - 2010 President, American Association for Stereotactic and Functional Neurosurgery

2012 Meeting Chair, Biennial meeting of the American Society for Stereotactic and Functional Neurosurgery, San Francisco

2011-2013 Scientific Program Committee, Movement Disorders Society

Honors

1983 Phi Beta Kappa Society

2001 and 2010 Rosegay teaching award for excellence in clinical teaching (awarded by UCSF residents)

2004 Dystonia Doctor of Excellence Award from the Dystonia Medical Research Foundation

2013 Named as one of ten finalists for an international competition in neuroprosthetics, the Israeli B.R.A.I.N prize

2013 Nominee for UCSF academic senate Distinction in Mentoring (DIM) award

2014 Distinguished Alumni Award, Catlin Gabel School, Portland OR

2018 Honored Guest of the biennial meeting of the American Society for Stereotactic and Functional Neurosurgery (Denver, CO).

**C. Contribution to Science**1. Understanding of basal ganglia-thalamocortical circuits in movement disorders, and mechanisms of therapy in humans. Over the past 15 years, the understanding of network dysfunction in Parkinson’s disease has emphasized the role of synchronized oscillatory neuronal activity in the basal ganglia. However, the effects of this synchronization on cortical function, and in general the nature of physiological changes in the cortex in PD, have been unknown. To address this, I introduced the method of combined cortical/basal ganglia recording in humans undergoing neurosurgery for movement disorders. Cortical recording is accomplished with flexible electrocorticography (ECoG) electrodes strips, advanced through the standard surgical exposure used for clinically indicated deep brain implants. My laboratory discovered a specific type of dysfunction in the primary motor cortex in PD, in which population spiking, as measured by the amplitude of broadband gamma in the power spectrum of the ECoG potential, is excessively coupled to the phase of the dominant motor beta rhythm (a). We believe that this constrains the motor cortex in an inflexible pattern of activity in which it is less able to respond to executive commands to move. We also demonstrated the same phenomenon non-invasively using scalp electroencephalography (d), and that similar patterns of cortical synchronization are prominent in primary dystonia (c). Further, we showed that therapeutic deep brain stimulation reverses this abnormality (b).

1. de Hemptinne C, Ryapolova-Webb ES, Air EL, Garcia PA, Miller KJ, Ojemann JG, Ostrem JL, Galifianakis NB, Starr PA. Exaggerated phase-amplitude coupling in the primary motor cortex in Parkinson disease. ***PNAS***110:4780-4785, 2013. PMCID: PMC3606991.
2. de Hemptinne C, Swann NC, Ostrem JL, Ryapolova-Webb ES, San Luciano M, Galifianakis NB, Starr PA. Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease. ***Nature Neuroscience*** 18(5):779-86, 2015. PMCID: PMC4414895.
3. Miocinovic S, de Hemptinne C, Qasim S, Ostrem JL, Starr PA. Patterns of Cortical Synchronization in Isolated Dystonia Compared With Parkinson Disease. **JAMA Neurology** 72(11):1244-51, 2015. PMCID: PMC4892933.
4. Swann NC, de Hemptinne C, Aron AR, Ostrem JL, Knight RT, Starr PA. Elevated synchrony in Parkinson disease detected with electroencephalography. **Annals of Neurology**. 2015 Nov;78(5):742-50. PMCID: PMC4623949.

2. Development of totally implanted bidirectional neural interfaces in humans. Much has been learned about human neurophysiology from intraoperative brain recordings during awake neurosurgery. However, acute recording techniques are limited by the extreme time constraints of the human operating room, the unnatural environment of the subject, the effects of recent sedatives or anesthetics, and acute changes in brain function produced by the “microlesion” effect of deep electrode insertion. Therefore, techniques for chronic invasive brain recording are urgently needed. My laboratory and clinical group has pioneered the use of a novel investigational bidirectional neural interface in humans with PD, the Activa PC+S device (Medtronic Inc). This is studied under a physician sponsored investigational device exemption. While several groups in the world have programs to use Activa PC+S, our program is distinctive in the implementation of a combined cortical and basal ganglia technique, using a permanently implanted cortical paddle over primary motor cortex. We first performed a preclinical study of this device over two years in a nonhuman primate (a), then launched the human study in November 2013. Ten PD patients have been implanted and recording in the first five described in detail (b). We have confirmed several prior findings from acute intraoperative recording, and leveraged the chronic nature of the recordings to demonstrate oscillatory signatures of the dyskinetic state (c). We have collaborated with Dr. Jose Carmena’s laboratory to test the use of an operant conditioning paradigm to train patients to voluntarily modulate their motor cortex beta rhythm (d).

1. Ryapolova-Webb E, P. Afshar, S, Stanslaski, T. Denison, de Hemptinne C, Bankiewicz K, and Starr PA, Chronic cortical and electromyographic recordings from a fully implantable device: preclinical experience in a nonhuman primate. ***J Neural Eng***. 11(1):016009, 2014. PMID: 24445430.
2. Swann NC, de Hemptinne C, Miocinovic S, Qasim S, Ostrem JL, Galifianakis NB, Luciano MS, Wang SS, Ziman N, Taylor R,. Chronic multisite brain recordings from a totally implantable bidirectional neural interface: experience in 5 patients with Parkinson's disease. **J Neurosurg**. 2017:1-12. PMCID: PMC5641233.
3. Swann, N.C., C. de Hemptinne, S. Miocinovic, S. Qasim, S.S. Wang, N. Ziman, J.L. Ostrem, M. San Luciano, N.B. Galifianakis, and Starr P.A, Gamma Oscillations in the Hyperkinetic State Detected with Chronic Human Brain Recordings in Parkinson's Disease. ***J Neurosci***, 2016. 36(24): p. 6445-58. PMCID: PMC5015781.
4. Khanna P, Swann NC, de Hemptinne C, Miocinovic S, Miller A, Starr PA, Carmena JM. Neurofeedback Control in Parkinsonian Patients Using Electrocorticography Signals Accessed Wirelessly With a Chronic, Fully Implanted Device. **IEEE Trans Neural Syst Rehabil Eng**. 2017;25(10):1715-24. PMCID: PMC5745199.

3. Invention and testing of improved technical method for implanting deep brain stimulators using real time interventional MRI. The effectiveness of deep brain stimulation for movement disorders is critically dependent on accurate lead placement. However, the traditional method for DBS placement, utilizing a stereotactic frame and physiological testing in awake patients, suffers from several shortcomings: the limited mechanical accuracy of the frames, inability to confirm accurate lead location with high resolution imaging intraoperatively, and the fact that some categories of patients (including children with dystonia) have difficulty with the awake, physiologically guided surgical approach. We developed an alternative surgical methodology, with new hardware and software designed to accurately implant leads within the bore of a high field MRI (a,b). The approach involves a skull mounted aiming device with four degrees of freedom, which is aligned using real time MR. Patients are under general anesthesia throughout. We have shown that the accuracy of placement of DBS leads is twice that of the traditional stereotactic method, and clinical outcomes are similar to standard frame-based techniques (c). Over 35 surgical groups worldwide have adopted this method since FDA approval in 2010, and our platform is increasingly applied to cell and drug infusion therapies and laser ablation, as well as DBS insertion.

1. Starr PA, Markun LC, Larson PS, Volz MM, Martin AJ, Ostrem JL. Interventional MRI-guided deep brain stimulation in pediatric dystonia: first experience with the ClearPoint system. **Journal of Neurosurg Pediatrics** 14(4):400-8, 2014. PMID: 25084088.
2. Starr PA, Martin AJ, Ostrem JL, Talke P, Levesque N, Larson PS Subthalamic nucleus deep brain stimulator placement using high-field interventional magnetic resonance imaging and a skull-mounted aiming device: technique and application accuracy. **Journal of Neurosurgery** 112(3):479-90, 2010. PMCID: PMC2866526.
3. Ostrem JL, Ziman N, Galifianakis NB, Starr PA, Luciano MS, Katz M, Racine CA, Martin AJ, Markun LC, Larson PS. Clinical outcomes using ClearPoint interventional MRI for deep brain stimulation lead placement in Parkinson's disease. **Journal of Neurosurgery** 124(4):908-16, 2016. PMID: 26495947.

4. Clinical trials of surgical interventions in movement disorders. For basal ganglia surgery in movement disorders, several alternative targets for intervention exist. For example, for PD, both GPi-DBS and STN-DBS have efficacy for motor signs. Our group was the lead implanting group for the largest randomized trial of DBS ever performed, in VA cooperative studies (#468) program, “A randomized trial of GPi versus STN DBS in PD”. This study showed that DBS at the two targets have equivalent motor benefits, but that the profile of mood and cognitive side effects favor the GPi target (a). This work has had a major role in changing clinical practice in the United States. As in PD, there has also been uncertainty regarding target choice in the treatment of primary dystonia. While GPi has been the empiric target, our group showed that GPi stimulation in segmental dystonic patients can result in a subtle bradykinesia in limbs that were previously normal. Working with Dr. Jill Ostrem, I launched the first prospective trial of STN-DBS in primary dystonia, showing equivalent motor benefits as GPi DBS, but without bradykinetic adverse effects (b).

1. Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, Marks WJ, Jr., Rothlind J, Sagher O, Moy C, Pahwa R, Burchiel K, Hogarth P, Lai EC, Duda JE, Holloway K, Samii A, Horn S, Bronstein JM, Stoner G, Starr PA, Simpson R, Baltuch G, De Salles A, Huang GD, Reda DJ. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. **N Engl J Med**. 2010;362(22):2077-91. PMID: 20519680.
2. Ostrem JL, Racine CA, Glass GA, Grace JK, Volz MM, Heath SL, Starr PA. Subthalamic nucleus deep brain stimulation in primary cervical dystonia. ***Neurology*** 76:870-878, 2011. PMID: 21383323.
3. Ostrem JL, San Luciano M, Dodenhoff KA, Ziman N, Markun LC, Racine CA, de Hemptinne C, Volz MM, Heath SL, Starr PA. Subthalamic nucleus deep brain stimulation in isolated dystonia: A 3-year follow-up study. **Neurology** 88(1):25-35, 2017. PMID:27903810.

**Complete list of first-authored and senior-authored published works available at:**

<http://www.ncbi.nlm.nih.gov/sites/myncbi/philip.starr.1/bibliography/41163825/public/?sort=date&direction=descending>

**D. Additional Information: Research Support and/or Scholastic Performance**  
Ongoing Research Support

1 UH3 NS100544-01      Starr (PI)  09/30/16 – 06/30/21     4.0 cal months

NIH/NINDS

**Closed loop deep brain stimulation for Parkinson's disease**

The goal of this project is to perform a small clinical trial of closed loop deep brain stimulation in Parkinson’s disease. Patients are implanted with a second-generation bidirectional neural interface, Activa RC+S, attached to permanent cortical and subthalamic nucleus electrodes. The study will address key questions needed to inform subsequent design of neural interfaces, including the utility of cortical versus subthalamic signal detection, and selection of frequency bands for optimal control signals.

2 R01 NS090913-05A1 Starr (PI) 02/01/19 – 01/31/24 3.0 cal months

NIH/NINDS $250,000

**The motor network in Parkinson's disease: mechanisms of therapy**

The goal is to understand the mechanisms of globus pallidus deep brain stimulation, at very fast time scales, using electrocorticography (ECoG). To perform longitudinal studies with ECoG, we ulilize a novel totally implanted bidirectional neural interface (Summit RC+S) attached to permanent cortical and basal ganglia electrodes, in humans undergoing deep brain stimulation therapy.

1R01MH114854-01 (MPI: Lazaro-Munoz, Goodman, McGuire)  09/01/17 – 08/31/21 0.12 cal month

NIH/NIMH (Lead Institution: Baylor College of Medicine) $340,485

**Neuroethics of aDBS Systems Targeting Neuropsychiatric and Movement Disorders**

This study aims to identify and empirically examine pressing neuroethics issues related to the use of adaptive deep brain stimulation (aDBS) systems in clinical trials for the treatment of neuropsychiatric and movement

disorders.

UH3 NS109556-01 (MPI: Chang and Starr)12/01/2018 – 11/30/2023        1.2 cal months

NIH/NINDS                                                                       $1,011,508

**Technology development for closed-loop deep brain stimulation to treat refractory neuropathic pain**

The major goal of this project is to develop data-driven algorithms to treat chronic pain using a novel neural interface device towards the goal of adaptive closed-loop deep brain stimulation.

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Bledsoe, Ian Owen

eRA COMMONS USER NAME (credential, e.g., agency login): IBLEDSOE

POSITION TITLE: Assistant Professor of Neurology

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

| INSTITUTION AND LOCATION | DEGREE  (if applicable) | Completion Date  MM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| Northwestern University, Evanston, IL | B.M./B.A., *Magna cum laude* | 06/2002 | Philosophy, Violin Performance |
| University of Pittsburgh School of Medicine, Pittsburgh, PA | M.D. | 05/2009 | Medicine |
| University of Pittsburgh Medical Center, Pittsburgh, PA  Stanford University School of Medicine  Stanford University School of Medicine  Rush University Medical Center  Rush University | M.S. | 06/2010  06/2013  06/2014  06/2016  06/2016 | Medical Intern    Neurology Residency  Clinical Neurophysiology Fellowship  Movement Disorders Fellowship  Clinical Research |

**A. Personal Statement**

I am neurologist with subspecialty training in movement disorders and a particular interest in dystonia. I have clinical expertise in the range of dystonias, including cervical and generalized dystonia. I have an active botulinum toxin injection clinic and evaluate patients with dystonia for deep brain stimulation implantation and programming. My clinical experience enables me to diagnose dystonia, administer rating scales, and will improve success of recruitment given direct patient care. In addition to movement disorders training, I have subspecialty training in clinical neurophysiology. My research background includes the study of movement disorders using multimodal neuroimaging techniques, including structural MRI and diffusion tensor imaging.

**B. Positions and Honors**

**Positions and Employment**

**2009-2010 Intern, Department of Internal Medicine, University of Pittsburgh Medical Center**

**2010-2013 Resident, Department of Neurology, Stanford University School of Medicine, Stanford, CA**

**2013-2014 Fellow, Department of Neurology, Stanford University School of Medicine, Stanford, CA**

**2014-2016 Fellow, Department of Neurological Sciences, Rush University, Chicago, IL**

**2016- Assistant Professor of Neurology, University of California, San Francisco**

**2019- Associate Medical Director, UCSF Movement Disorder and Neuromodulation Center**

**Other Experience and Professional Memberships**

**2010- Member, American Academy of Neurology**

**2013- Diplomate, American Board of Psychiatry and Neurology**

**2014- Member, International Parkinson’s Disease and Movement Disorders Society**

**2016- Member, Performing Arts Medical Association**

**Honors**

1997-2002 Dean's List, Northwestern University, Evanston, Illinois

2000-2002 Margaret Morris Henderson Scholarship Fund for Academic and Musical Excellence

2005 Phi Beta Kappa National Honor Society, Northwestern University

2007-2009 Recipient, Joseph Collins Foundation Grant

2013 Stanford Neurology Clerkship Teaching Award

2015 American Academy of Neurology Annual Meeting Travel Grant

2017 Keynote Speaker, American Parkinson Disease Association West Coast Parkinson’s

Educational Forum

2018 Parkinson Study Group annual meeting and symposium travel fellowship award

**C. Contribution to Science**

1. Investigation of morphometrics of the corpus callosum in Parkinson’s disease cognitive impairment. This study demonstrated reduced corpus callosum volume on structural MRI scans in a cohort of Parkinson’s disease participants as compared to healthy controls, with greater volume loss seen in the most cognitively impaired Parkinson’s disease cohort. Corpus callosal volume loss additionally showed a significant relationship with performance in a number of cognitive domains. Volume loss in the corpus callosum has not previously been reported in Parkinson’s disease, and these findings may suggest new avenues of research into the way that disrupted structural connectivity contributes to Parkinson’s disease cognitive impairment. Morphometric evaluations were expanded to thickness and area measurements in the corpus callosum in Parkinson’s disease cognitive impairment as well.
   1. Goldman JG, Bledsoe IO, Merkitch D, Dinh V, Bernard B, Stebbins GT. Corpus callosal atrophy and associations with cognitive impairment in Parkinson disease. Neurology. 2017;88:1265-1272
   2. Bledsoe IO**,** Merkitch D, Stebbins GT, Bernard, BA, Goldman, JG. Corpus callosum thickness and area in Parkinson’s disease. Poster session presented at the 20th International Congress of Parkinson’s Disease and Movement Disorders; 2016 June 22; Berlin, Germany
2. A second study evaluating diffusion tensor imaging (DTI) changes in the corpus callosum in Parkinson’s disease cognitive impairment demonstrated altered DTI scalar values in the anterior portions of the corpus callosum and significant relationships among DTI measures and performance in several cognitive domains. This is the first report of alteration in axial diffusivity (AD) and radial diffusivity (RD) in the corpus callosum in Parkinson’s disease cognitive impairment, expanding the description of microstructural changes in white matter in Parkinson’s disease, and suggesting further alteration in structural connectivity which may contribute to cognitive impairment in this cohort.
   1. Bledsoe IO, Stebbins GT, Merkitch D, Goldman JG. White matter abnormalities in the corpus callosum with cognitive impairment in Parkinson disease. Neurology. 2018; 11;91(24):e2244-55
3. A recent study evaluated clinical characteristics and phenomenological features of stimulation-induced dyskinesias in patients with isolated dystonia implanted with STN DBS.
   1. Dodenhoff, K., Bledsoe, I.O., Ostrem, J. S. Phenomenology and management of subthalamic stimulation-induced dyskinesia in a series of patients with isolated dystonia. Poster session presented at the 22nd International Congress of Parkinson's Disease and Movement Disorders; 2018 October; Hong Kong

**Complete List of Published Work in MyBibliography:**

<https://www.ncbi.nlm.nih.gov/myncbi/1ZuUJzh-ZgzQe/bibliography/public/>

**D. Research Support**

**Ongoing Research Support**

|  |  |  |  |
| --- | --- | --- | --- |
| 1. | Co-Investigator | 10 % effort | Rosen (PI) |
| Philanthropic/Private Funding Source | | 07/01/2018 | 07/01/2020 |
| Parkinson's Spectrum Project | |  |  |
| The Parkinson's Spectrum Project is a multi-investigator collaborative effort aimed at improving diagnostic accuracy and recognizing prodromal features of different forms of parkinsonism, including Parkinson's disease, Progressive Supranuclear Palsy, Corticobasal Syndrome, Multiple System Atrophy, Lewy Body Dementia, and Vascular Parkinsonism using quantitative motor, cognitive, psychiatric, and autonomic assessment, imaging markers including MRI and Tau-PET, and fluid biomarkers. | | | |
| I am involved in direct examination and clinical testing of study participants, committee consensus diagnosis, study design, and data analysis | | | |

|  |  |  |  |
| --- | --- | --- | --- |
| 2. Voyager Therapeutics | Neurologist Clinical Rater | 2-8 % effort | Site PI: Christine/Larson (PI) |
|  | | 05/01/2018 | 07/01/2020 |
| A Randomized, Placebo Surgery Controlled, Double-blinded, Multi-center, Phase 2 Clinical Trial, Evaluating the Efficacy and Safety of VY-AADC02 in Advanced Parkinson’s Disease with Motor Fluctuations (Short Title: AADC in Advanced PD Trial – ADAPT).This is a multi-site gene therapy clinical trial investigating use of intra-putaminal injection of VY-AADC02 to evaluate improvement in motor fluctuations in participants with Parkinson's disease. | | | |
| Neurologist clinical rater involved in testing of clinical markers of severity of parkinsonism. | | | |

3.

|  |  |  |  |
| --- | --- | --- | --- |
| UH3NS100544 | Clinical Neurologist | 5 % effort | Starr (PI) |
| NIH/NINDS | |  |  |
| Closed loop deep brain stimulation for Parkinson's disease | |  |  |
| This is a trial aiming to develop closed-loop DBS algorithms using an investigational neural interface (Medtronic Activa RC+S). | | | |
| Clinical neurologist involved in DBS programming and clinical care of trial participants. | | | |

**Completed Research Support**

MH18951 Brent (PI) 07/01/05-09/01/05

Clinical research training grant in child psychiatry. Funding from this grant was utilized for mentored research in a retrospective chart review evaluating children with psychogenic non-epileptic seizures.

Role: Student investigator

# Letters of Support or Collaboration